

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
19 September 2002 (19.09.2002)

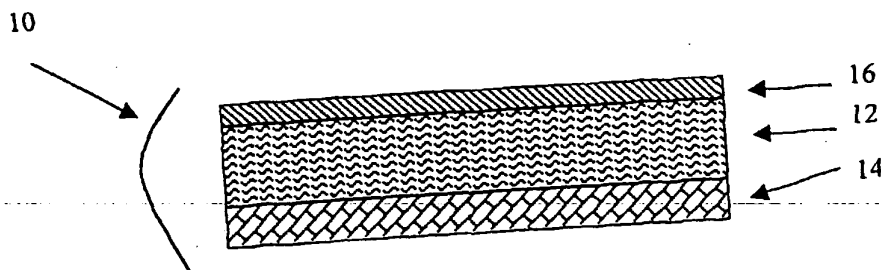
PCT

(10) International Publication Number
WO 02/072081 A1

- (51) International Patent Classification⁷: **A61K 31/04**, (74) Agent: **FIELD, Bret, E.**; Bozicevic, Field & Francis, L.L.P., 200 Middlefield Road, Suite 200, Menlo Park, CA 94025 (US).
- (21) International Application Number: **PCT/US02/05641**
- (22) International Filing Date: **22 February 2002 (22.02.2002)**
- (25) Filing Language: **English**
- (26) Publication Language: **English**
- (30) Priority Data: **12 March 2001 (12.03.2001) US 60/275,213**
- (71) Applicant (for all designated States except US): **TEIKOKU PHARMA USA, INC. [US/US]; 745-D Camden Avenue, Campbell, CA 95008-4146 (US).**
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **SHUDO, Jutaro [JP/US]; 4829 Vanderbilt Drive, San Jose, CA 95130 (US). MORI, Ichiro [JP/US]; 1570 Calle De Aida, San Jose, CA 95118 (US).**
- (81) Designated States (national): **AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.**
- (84) Designated States (regional): **ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).**
- Published: **with international search report**

[Continued on next page]

(54) Title: **TOPICAL PATCH PREPARATION CONTAINING A DELAYED-TYPE HYPERSENSITIVITY INDUCER AND METHODS FOR USING THE SAME**



WO 02/072081 A1

(57) Abstract: Topical patch preparations that contain a delayed-type hypersensitivity inducer, e.g., 1-dichloro-2,4-dinitrobenzene (DNCB), and methods for using the same are provided. The subject topical patch preparations are made up of an adhesive gel composition that is present on a support, where the adhesive gel composition includes the delayed-type hypersensitivity inducer, a water-soluble polymer gel, water and a water holding agent. In using the subject topical patch preparations, the topical patch preparations are applied to a skin surface of a subject and maintained at the site of application for a period of time sufficient for an effective amount of the delayed-type hypersensitivity inducer to be administered to the subject, where this maintenance period typically does not exceed about 60 minutes. The subject invention finds use in a variety of applications where the administration of a delayed-type hypersensitivity inducer is desired, and is particularly suited for use in the treatment of HIV associated disease conditions, e.g., AIDS.

BEST AVAILABLE COPY

WO 02/072081 A1



— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

**TOPICAL PATCH PREPARATION CONTAINING A DELAYED-TYPE
HYPERSENSITIVITY INDUCER AND METHODS FOR USING THE SAME**

CROSS REFERENCE TO RELATED APPLICATIONS

5 Pursuant to 35 U.S.C. § 119 (e), this application claims priority to the filing date of the United States Provisional Patent Application Serial No. 60/275,213 filed March 12, 2001; the disclosures of which are herein incorporated by reference.

INTRODUCTION

10 Field of the Invention

The field of this invention is delayed-type hypersensitivity inducing agents.

Background of the Invention

15 The number of Human Immunodeficiency Virus (HIV) patients worldwide has been increasing rapidly in recent years, and is said to be approximately 33 million (WHO; end of 1998). Against this backdrop, there is a rush to develop a vaccine for HIV. However, but because of the mutation of the configuration of the virus following infection, a feature of HIV, an accurate vaccine has not yet been found. In addition, although many therapeutic
20 medications for HIV have been developed, none completely cure HIV. Furthermore, current AIDS drugs (protease inhibitors, non-nucleoside reverse transcriptase inhibitors, nucleoside reverse transcriptase inhibitors, etc.) employ complex techniques. Long-term administration of these agents causes patients to suffer persistent adverse events, such as anemia, peripheral neuritis, pancreatitis, nausea, and headaches. Also, the possibility of long-term
25 administration resulting in drug resistance cannot be ruled out. Yet another disadvantage of current treatment modalities is cost, in that current therapeutic medications for HIV are extremely expensive, often ranging between \$15,000 to \$20,000 per person per year, which necessarily limits patient access.

30 One type of agent that represents an effective alternative to current HIV treatment modalities is the delayed-type hypersensitivity (DTH) inducing agent, which type of agent has been researched as an immunomodulator that elicits immunological response in HIV patients by increasing the activity of the immune system cells in the body. Delayed-type hypersensitivity inducers are substances that induce Type 4 hypersensitivity when they come

into contact with human skin, and they include trinitrobenzene sulfonic acid, picryl chloride(PC), 2,4-dinitrofluorobenzene(DNFB), and 1-chloro-2,4-dinitrobenzene (DNCB). Of these, DNCB has been widely used in the treatment of HIV and in immunological research, and the present invention focuses on DNCB as a DTH inducer in many
5 embodiments, as described in greater detail below.

DNCB was discovered in Germany before World War II. Research conducted in the 1950s in the US demonstrated that DNCB is not carcinogenic. Later, in the 1970s, safety research was conducted in various types of animals. DNCB is generally known to be a powerful, delayed allergy-inducing skin irritant in humans, and is used in, among other
10 things, immunological tests of skin diseases.

Research on DNCB therapy in HIV patients began slowly from the middle of the 1980s, and research on DNCB therapy in HIV patients was conducted in the first half of the 1990s, from which DNCB was claimed to be effective for treating HIV. However, this claim was not proved. In the latter half of the 1990s, the development of PCR analysis technology
15 began to confirm the efficacy of DNCB in HIV patients. In addition, DNCB was also previously investigated as a possible treatment for cancer: tests were conducted in which DNCB was applied locally to induce a delayed allergic reaction and thereby utilize its immunity inducing capabilities. However, these findings have not been put to practical use. Furthermore, DNCB has been used in, among other things, the treatment of warts.

20 A method for using DNCB in HIV patients that has been employed in recent years has been to dissolve the DNCB in an acetone solvent and impregnate a gauze-like cloth with the resulting product and apply this to the skin. This topical preparation is then dried, covered and left to stand for several hours (typically at least 8 hours). This long application time means that an HIV patient would be restricted for at least 8 hours, a fairly long time,
25 which would prevent that person from leading the same lifestyle as a healthy person.

There is considerable interest, therefore, in the development of a topical DTH inducing agent composition that could efficiently deliver an effective amount of a DTH inducing agent to a host in a short period of time.

Relevant Literature

30 References of interest include: Stricker et al. Dendritic cells and dinitrochlorobenzene (DNCB): A new treatment approach to AIDS. *Immunol Letters* 1991;29:191-196; Stricker et al. Pilot study of topical dinitrochlorobenzene (DNCB) in human immuno deficiency virus infection. *Immunol Letters* 1993;36:1-6; Stricker et al.

WO 02/072081

- Topical dinitrochlorobenzene in HIV disease. *J Am Acad Dermatol* 1993;28:796-797; Stricker et al. Clinical and immunologic evaluation of HIV-infected patients treated with dinitrochlorobenzene (DNCB). *J Am Acad Dermatol* 1994;31:462-466; Stricker RB, Goldberg B, Mills LB, Epstein WL. Improved results of delayed-type hypersensitivity skin testing in HIV-infected patients treated with topical dinitrochlorobenzene(DNCB). *J Am Acad Dermatol* 1995;33:608-611; Stricker & Goldberg. Safety of topical dinitrochlorobenzene. *Lancet* 1995;346:1293; Stricker et al. Improved results of delayed-type hypersensitivity skin testing in HIV-infected patients treated with topical dinitrochlorobenzene. *J Am Acad Dermatol* 1996;35:491-493; Stricker et al. Decrease in viral load associated with topical dinitrochlorobenzene therapy in HIV disease. *Res Virol* 1997;148:343-348; Traub et al. Topical immune modulation with dinitrochlorobenzene (DNCB) in HIV disease: A controlled trial from Brazil. *Dermatology* 1997;195:369-373; Stricker et al. Topical immune modulation (TIM): A novel approach to the immunotherapy of systemic disease. *Immunol Letters* 1997;59:145-150; Oracion et al. DNCB treatment of HIV-infected patients leads to beneficial immunologic outcomes, reduced viral load, and improved measures of quality-of-life. *J Invest Dermatol* 1998;110:476.

SUMMARY OF THE INVENTION

- Topical patch preparations that contain a delayed-type hypersensitivity inducer, e.g., 1-dichloro-2,4-dinitrobenzene (DNCB), and methods for using the same are provided. The subject topical patch preparations are made up of an adhesive gel composition that is present on a support, where the adhesive gel composition includes the delayed-type hypersensitivity inducer, a water-soluble polymer gel, water and a water holding agent. In using the subject topical patch preparations, the topical patch preparations are applied to a skin surface of a subject and maintained at the site of application for a period of time sufficient for an effective amount of the delayed-type hypersensitivity inducer to be administered to the subject, where this maintenance period typically does not exceed about 60 minutes. The subject invention finds use in a variety of applications where the administration of a delayed-type hypersensitivity inducer is desired, and is particularly suited for use in the treatment of HIV associated disease conditions, e.g., AIDS.

BRIEF DESCRIPTION OF THE FIGURES

WO 02/072081

Fig. 1 provides a cross-sectional view of a topical patch preparation according to the invention.

Figs. 2 and 3 provide schematic representations of the manufacturing process for topical patch preparations of the invention.

5

DESCRIPTION OF THE SPECIFIC EMBODIMENTS

Topical patch preparations that contain a delayed-type hypersensitivity inducer, e.g., 1-dichloro-2,4-dinitrobenzene (DNCB), and methods for using the same are provided. The subject topical patch preparations are made up of an adhesive gel composition that is present on a support, where the adhesive gel composition includes the delayed-type hypersensitivity inducer, a water-soluble polymer gel, water and a water holding agent. In using the subject topical patch preparations, the topical patch preparations are applied to a skin surface of a subject and maintained at the site of application for a period of time sufficient for an effective amount of the delayed-type hypersensitivity inducer to be administered to the subject, where this maintenance period typically does not exceed about 60 minutes. The subject invention finds use in a variety of applications where the administration of a delayed-type hypersensitivity inducer is desired, and is particularly suited for use in the treatment of HIV associated disease conditions, e.g., AIDS. In further describing the subject invention, the topical patch preparations are described first in greater detail, followed by a review of representative applications in which the subject topical patch preparations find use.

Before the subject invention is described further, it is to be understood that the invention is not limited to the particular embodiments of the invention described below, as variations of the particular embodiments may be made and still fall within the scope of the appended claims. It is also to be understood that the terminology employed is for the purpose of describing particular embodiments, and is not intended to be limiting. Instead, the scope of the present invention will be established by the appended claims.

In this specification and the appended claims, singular references include the plural, unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which this invention belongs.

WO 02/072081

TOPICAL PATCH PREPARATIONS

As summarized above, the subject invention is directed to topical patch preparations of a delayed-type hypersensitivity inducer agent. The topical patch preparations of the subject invention are characterized by having an effective amount of the delayed type hypersensitivity inducer agent present in a gel adhesive base. Figure 1 provides a representation of a topical patch preparation described according to the subject invention. As can be seen in Figure 1, this representative topical patch preparation 10 contains a gel adhesive base 12 present on a support 14. Each of these components is now described in greater detail.

The gel adhesive base which serves as the delayed-type hypersensitivity inducer retaining layer, is made up of the delayed-type hypersensitivity inducer that is present in, e.g., dissolved in or dispersed in, and adhesive gel base. By "delayed-type hypersensitivity (DTH) inducers" is meant an immunomodulator that elicits immunological response in a subject, such as HIV patients, by increasing the activity of the immune system cells in the body. Delayed-type hypersensitivity inducers are substances that induce Type 4 hypersensitivity when they come into contact with human skin, and they include, but are not limited to: trinitrobenzene sulfonic acid, picryl chloride (PC), 2,4-dinitrofluorobenzene(DNFB), and 1-chloro-2,4-nitrobenzene (DNCB). In many embodiments, the delayed-type hypersensitivity inducer is DNCB.

The amount of DTH inducer that is present in the adhesive gel base is an amount sufficient to administer to a subject an effective amount of the agent when applied to a skin surface of the subject, as described in greater detail below. In many embodiments, the amount of DTH inducer present in the adhesive gel base ranges from about 0.01 to 10.0 % (w/w), sometimes from about 0.05 to 10.0 % (w/w), usually from about 0.1 to 5.0 % (w/w) and more usually from about 0.2 to 3.0 % (w/w).

The adhesive gel base that includes the DTH inducer, as described above, is made up of a water-soluble high molecular weight substance, water and a water retaining agent. In certain embodiments, the adhesive gel base may further include a cosolvent, e.g., an organic cosolvent. Each of these components is now described separately in greater detail.

Water-soluble high molecular weight substances of interest include water-soluble polymers, where polymers of interest include, but are not limited to: gelatin, starch, agar, mannan, alginic acid, polyacrylic acid, polyacrylate, dextrin, methylcellulose, sodium

WO 02/072081

methylcellulose, hydroxypropylcellulose, sodium carboxymethylcellulose, cellulose gum, carboxyvinyl polymer, polyvinyl alcohol, polyvinylpyrrolidone, Arabia gum, acacia, tragacanth gum, karaya gum, and starch acrylate copolymer or other starch sodium acrylate graft copolymers. Metallic salts of these, as well as the products of cross-linking these by means of organic or inorganic cross-linking agents, are also of interest. These water-soluble polymers can be used to bring out the properties and characteristics of the other starting materials used in the adhesive gel composition, and in practice can be used alone or in combinations of 2 or more. The amount of water soluble high molecular weight substance(s) present in the adhesive gel base generally ranges from about 0.5 to 20, usually from about 2 to 20 % (w/w).

While any convenient water may be employed as the water component, of interest are distilled water or ion-exchange water or the like, which is preferred in many embodiments of the subject invention. The amount of water present in the gel adhesive is sufficient to impart the desired physical properties to the gel adhesive, and to improve the swelling of the horny or keratinized layer of the skin to thereby improve the permeability or penetration of the DTH inducing agent(s), where the amount of water in the gel composition generally ranges from about 10 to 80%, usually from about 30 to 60% (w/w).

The water-retaining agent or water-holding agent of the subject adhesive gel compositions is any agent that is capable of at least diminishing the volatilization of water contained in the adhesive gel base so that the water content in the adhesive gel base is maintained at least a substantially constant, if not constant, level during storage and use of the preparation. One or more water-retaining agents may be employed in the subject compositions, where the amount of water-retaining agent present in the adhesive gel base generally ranges from about 1 to 70%, more preferably 10 to 60% by weight. Examples of suitable water-retaining or water-holding agents include, but are not limited to: 1 or more types of polyvalent or polyhydric or sugars or alcohols, such as glycerin, sorbitol, propylene glycol, diethylene glycol, 1,3-butylene glycol, and ethylene glycol, and the like.

In addition, the subject gel base compositions may also include a cosolvent, where the cosolvent is generally an organic cosolvent. Examples of DNCB cosolvents of interest include, but are not limited to, n-methyl-2-pyrrolidone, crotamiton, ethyl alcohol, methyl alcohol, polyethylene glycol (e.g., low molecular weight polyethylene glycol, such as PEG 600 or lower, e.g., 500, 400, 300, 200, 100 etc and blends thereof, and acetone, where n-methyl-2-pyrrolidone, polyethylene glycol and crotamiton are of particular interest. The

WO 02/072081

cosolvent may be made up of a simple component or be in combination of two or more components.

Furthermore, in addition to the aforementioned ingredients, various additives that are used in ordinary topical water-soluble patch preparations may also be suitably compounded as needed, including inorganic substances such as kaolin, bentonite, and titanium dioxide; 5 preservatives such as paraben; anionic, cationic, and nonionic surfactants; metallic aluminum crosslinking agents such as aluminum chloride, dried aluminum hydroxide gel, and dihydroxyaluminum aminoacetate; oils such as jojoba oil and castor oil; chelating agents such as EDTA; pH regulators such as malic acid, tartaric acid, and diisopropanolamine; 10 alcohols such as ethanol; moisture retaining agents such as hyaluronic acid, aloe extract, and urea; and other perfumes and coloring agents.

The pH of the gel base composition typically is one that lies in a physiologically acceptable range, where the pH typically ranges from about 4.0 to 7.0 and more typically ranges from about 4.0 to 6.0.

15 As mentioned above, the adhesive gel composition containing the one or more active ingredients is typically present on a support or backing. The support is generally made of a flexible material which is capable of fitting in the movement of human body and includes, for example, various non-woven fabrics, woven fabrics, spandex, flannel, or a laminate of these materials with polyethylene film, polyethylene glycol terephthalate film, polyvinyl 20 chloride film, ethylene-vinyl acetate copolymer film, polyurethane film, and the like.

In addition to the adhesive gel composition and the support layer, the subject topical patches may also include a release film 16 on the surface of the gel layer opposite the backing that provides for protection of the gel layer from the environment. The release film may be any convenient material, where representative release films include polyesters, such 25 as PET or PP, and the like.

In many embodiments, the patch is present in a sealed package. Generally, the sealed package is fabricated from a packaging material that includes a layer made out of a material capable of preventing passage of moisture, oxygen and other agents, i.e., the package includes in a moisture/oxygen barrier material. Any suitable barrier material may be 30 employed, where barrier materials of interest include metallic layers, e.g., aluminum, where in many embodiments, the barrier layer is an aluminum layer. This barrier layer has a thickness sufficient to provide for the barrier function, where the thickness typically ranges from about 5 to 15, usually from about 6 to 10 μm . In many embodiments, the package is a

WO 02/072081

laminate of the barrier layer in combination with one or more additional layers, e.g., polymeric layers, paper layers, etc. A representative aluminum containing package that may be used with the subject patch preparations is sold by Dainippon Printing Co., Ltd. (Kyoto, Japan).

5 The topical patch preparations may be fabricated using any convenient protocol. One convenient protocol for fabrication of the subject patches includes preparing a gel adhesive paste through the uniform mixing of the aforementioned ingredients and then coating the paste onto the support, followed by cutting of the resultant product to the specified size to obtain the desired topical patch preparation. The resultant topical patch preparation is then
10 heat-sealed, typically several sheets to a package, using a packaging material containing an aluminum layer, as described *supra*, to obtain the sealed topical patch. For a more detailed description of the fabrication protocol, see U.S. Patent No. 5,827,529; the disclosure of which is herein incorporated by reference.

15 In a representative fabrication protocol, the base used in the present invention is produced by using a mixer to uniformly blend the aforementioned ingredients by means of any convenient protocol into a paste, which is then spread by means of a spreader onto a backing or support material. As indicated above, the support material may be, for example, paper, or a woven or nonwoven cloth made of PET or PP or some other polyester fiber. For protection, the surface thereof is then covered with a release film of a polyester such as PET
20 or PP. These steps are illustrated in Figure 2.

25 The resulting product is then cut to the specified size to obtain the desired topical patch preparation composition. The shape of the patch may vary, where representative shapes include square, rectangle, oval, circle, etc. The size of the patch may also vary, where in many embodiments the size ranges from about 1 to 200 cm², and in many embodiments from about 10 to 100 cm², usually from about 20 to 50 cm², e.g., 25 cm². The weight of the base in the final topical patch should be 300 to 1500 g/m², and preferably 600 to 1000 g/m². This water-soluble topical patch preparation is then packaged by means of a heat seal in a packaging material that includes a layer of aluminum to obtain the final product, as shown in
Figure 3.

30 It should be noted that the above manufacturing protocols are merely representative. Any convenient protocol that is capable of producing the subject topical patch preparations, as described above, may be employed.

WO 02/072081

METHODS OF USING PATCH PREPARATIONS

The subject patch preparations find use in the topical delivery of DTH inducing agents, e.g., DNCB, to a host. By "topical delivery" is meant delivery via absorption through the skin. In using the subject topical patch preparations to topically administer a DTH inducing agent to the host, the topical preparation is applied to a skin surface and maintained at the site of application for a period of time sufficient for the desired amount of DTH inducing agent to be delivered to the host. In many embodiments, the period of time required to deliver the desired amount of agent is short, generally not exceeding about 60 minutes, usually not exceeding about 30 minutes and in many embodiments not exceeding about 15 minutes. However, the period of time during which the preparation is maintained at the application site is, in many embodiments, at least about 1 minute, usually at least about 3 minutes and more usually at least about 5 minutes.

The patch may be administered to any convenient topical site. Topical sites of interest include, but are not limited to: arms, leg, torso, etc. The surface area that is covered by the topical patch preparation following application must be sufficient to provide for the desired amount of agent administration, and in many embodiments ranges from about 1 to 200 cm², and in many embodiments from about 10 to 100 cm², usually from about 20 to 50 cm², e.g., 25 cm². In practicing the subject methods, a topical patch may be applied a single time or a plurality of times over a given time period, e.g., the course of the disease condition being treated, where the dosing schedule when a plurality of patches are administered over a given time period may be daily, weekly, biweekly, monthly, etc.

UTILITY

The above described patches and methods find use in any application in which the administration of an DTH inducing agent to a host is desired. Generally such hosts are "mammals" or "mammalian," where these terms are used broadly to describe organisms which are within the class mammalia, including the orders carnivore (e.g., dogs and cats), rodentia (e.g., mice, guinea pigs, and rats), and primates (e.g., humans, chimpanzees, and monkeys). In many embodiments, the hosts will be humans.

In many embodiments, the subject methods find use in the treatment of a disease condition. By treatment is meant at least an amelioration of the symptoms associated with the pathological condition afflicting the host, where amelioration is used in a broad sense to

WO 02/072081

refer to at least a reduction in the magnitude of a parameter, *e.g.* symptom, associated with the pathological condition being treated, such as viral load or side effects associated therewith. As such, treatment also includes situations where the pathological condition, or at least symptoms associated therewith, are completely inhibited, *e.g.* prevented from happening, or stopped, *e.g.* terminated, such that the host no longer suffers from the pathological condition, or at least the symptoms that characterize the pathological condition. As such, treatment includes both curing and managing a disease condition.

In many embodiments, the disease condition that is treated according to the subject methods is one that is a chronic disease. Chronic diseases of interest include, but are not limited to: chronic fatigue syndrome, systemic lupus erythematosus, leprosy, leishmaniasis, diseases associated with the presence of intracellular pathogenic agents (*e.g.*, viruses, bacteria), such as cytomegalovirus, Candida, Cryptococcus, Penumocystis carinii, and the like.

Of particular interest is the use of the subject methods in the treatment, *e.g.*, management, of immunocompromising disease conditions, and particularly HIV associated disease conditions, *e.g.*, AIDS. Treatment in the context of HIV associated diseases means improvement of quality of life, *e.g.*, via reduction in one or more symptoms, the occurrence of opportunistic infections, etc. In terms of quantifiable parameters associated with HIV disease conditions, the subject invention finds use in reducing viral load and/or increasing the population of natural killer cells, while varying the population of at least one of CD4 cells and CD8 cells. Such changes in quantifiable parameters are achievable with application times that do not exceed 15 minutes in length.

KITS

Also provided are kits, where the subject kits at least include one or more DTH inducing agent topical patch preparations, as described above. The subject topical patch preparations in the kits may be present in a package, as described *supra*. The topical patches of the kits are typically present in individual pouches or analogous containers, to preserve the composition of the patches until use. The subject kits also generally include instructions for how to use the patches in DTH inducing agent delivery to a host where the instructions typically include information about where to apply the patch, dosing schedules etc. In certain embodiments, the subject kits include instructions on how to use the patched to treat a particular disease condition with a DTH inducing agent. The instructions are generally

WO 02/072081

recorded on a suitable recording medium. For example, the instructions may be printed on a substrate, such as paper or plastic, etc. As such, the instructions may be present in the kits as a package insert, in the labeling of the container of the kit or components thereof (i.e. associated with the packaging or subpackaging) etc. In other embodiments, the instructions are present as an electronic storage data file present on a suitable computer readable storage medium, e.g. CD-ROM, diskette, etc.

The following practical and comparative examples are offered by way of illustration and not by way of limitation.

EXAMPLES

Practical and comparative examples are given below, but the manufacturing method is not limited thereby.

I. Preparation of Topical Patches

Practical Examples-A water-soluble polymer topical patch preparation in which DNCB has been compounded in an amount of 2%. 2% DNCB is dissolved in n-methyl-2-pyrrolidone, after which the ingredients are blended into uniformity and adjusted into a paste, which is then spread onto a PET nonwoven cloth to a weight of 850 g/m²; the resulting product is then laminated with a PP film and then cut into 5 cm squares. Finally, each individual DNCB patch is heat-sealed in packaging material containing aluminum foil to obtain the finished product. See Figs. 2 and 3.

Placebo -A water-soluble polymer topical patch preparation in which water was used in place of the DNCB in the practical example. The ingredients are blended into uniformity and adjusted into a paste, which is then spread onto a PET nonwoven cloth to a weight of 850 g/m²; the resulting product is then laminated with a PP film and then cut into 5 cm squares. Finally, each individual placebo patch is heat-sealed in packaging material containing aluminum foil to obtain the finished product. See Figs. 2 and 3. Table 1 summarizes the content of the practical and placebo compositions.

Table 1

Starting Material	Practical Example	Placebo
DNCB	2.0	---
Water	49.525	51.525

WO 02/072081

EDTA	0.1	0.1
Methylparaben	0.15	0.15
Tartaric acid	0.7	0.7
Sodium polyacrylate	5.0	5.0
Polyacrylic acid	4.0	4.0
n-methyl-2-pyrrolidone	2.0	2.0
Castor oil	2.0	2.0
Aluminum hydroxide	0.025	0.025
Cellulose gum	4.0	4.0
Glycerin	20.0	20.0
Sorbitol	10.0	10.0
Kaolin	0.5	0.5
Total	100.000	100.000
PH	4.5-5.0	4.5-5.0

*: All values are expressed in terms of % (w/w).

II. Stability Data

- 5 Stability data on the DNCB content in the practical example. The experiment was conducted in an environment of 25°C and 60% humidity. The results are shown in a comparison with the initial value, which was taken to be 100% and are provided in Table 2.

Table 2

10

	Initially	After 1 month	After 3 months	After 6 months	After 9 months
DNCB content	100%	99.5%	99.2%	99.0%	99.1%

III. Discoloration Test

- We measured the degree of discoloration for the stability of the DNCB water-soluble topical preparation in the practical example. The experiment was conducted in an environment of 25°C and 60% humidity. The results are shown in terms of the degree of discoloration relative to the initial value and are provided in Table 3.
- 15

Considerable difference: 3+

Visible difference: 2+

Slight difference: +

No change: -

20

WO 02/072081

Table 3

	Initially	After 1 month	After 3 months	After 6 months	After 9 months
Degree of discoloration	-	+	+	+	+

IV. Activity Assay

5

We applied the DNCB water-soluble topical patch preparation of the practical example to HIV patient volunteers to investigate its efficacy for HIV. We used the placebo water-soluble topical patch preparation for comparison.

- 10 We applied the patch preparation to the upper extremity of 5 volunteers for 8 hours (1 patient), 4 hours (1 patient), and 15 minutes (3 patients), and after 1 week collected and analyzed their blood. Viral Load (VL) measurements were taken by means of ultrasensitive HIV-1 RNA PCR analysis.

The results are shown below in Table 4.

15

Table 4

	Application Time	Skin irritation	CD4		CD8		NK		VL	
			Pre	Post	Pre	Post	Pre	Post	Pre	Post
Patient 1	8 hours	G4	110	129	622	632	60	32	45930	71676
Patient 2	4 hours	G3	257	248	1379	1562	70	74	< 20	< 20
Patient 3	15 minutes	G0	107	199	426	637	67	82	85615	1188
Patient 4	15 minutes	G0	253	226	747	767	24	34	23385	5720
Patient 5	15 minutes	G0	14	6	826	303	14	50	581655	68144

*1: CD4&CD8; T-Cell Subsets: NK, Natural Killer Cell: VL: Viral Load (RNA PCR)

*2: Skin Reaction Grade

Grade 4 (G4): Erythema, blistering and bulla formation

Grade 3 (G3): Erythema, blistering; no bulla

WO 02/072081

- Grade 2 (G2): Erythema covering entire patch area; no blistering
Grade 1 (G1): Mild erythema covering less than entire patch area
Grade 0 (G0): Minimal or no reaction at patch site

5 V. Discussion

Based on Tables 2 and 3, the DNCB in the water-soluble patch preparation is stable; discoloration was within a usable range, and practicality was sufficient. Table 4 shows that, in Patient 1, when the DNCB water-soluble patch preparation was applied for a long period of time (8 hours), considerable skin irritation occurred; CD4 and CD8 counts increased, but NK decreased, and VL increased. In Patient 2, the degree of skin irritation was less than for Patient 1. The NK count increased somewhat, and no significant change was seen in VL. For Patients 3 through 5, the time of application was short (15 minutes), and there was no skin irritation. However, the CD4 and CD8 counts exhibited changes, the NK count clearly increased, and the VL decreased dramatically, clearly demonstrating the suppression of the HIV blood concentration. Since DNCB immunological activation contributes to the increase in NK cells, it is also contributes to the decreased VL. Based on this information, it is meaningless to apply the DNCB water-soluble patch preparation for a long period of time; simply applying it to the skin for a short period (about 15 minutes) is extremely effective versus HIV, and is clearly practical. In addition, we simultaneously conducted a study in which a placebo was applied: there was no skin irritation, and absolutely no effect on HIV. This reconfirmed the clear effect of DNCB. Furthermore, when using the patch, simply applying it to the skin for a short period of time allows AIDS to be treated without a change in the lifestyle of the patient, who is therefore able to lead exactly the same lifestyle as a healthy person. In addition, concomitant use with other HIV therapeutic medications is also quite possible. Research has been conducted for some time into the adverse events of DNCB, and there have not been any reports to date of cases of life-threatening adverse events, such as carcinogenicity. Moreover, the DNCB water-soluble topical patch preparation of the present invention is only applied once a week, so treatment is possible at a cost of approximately \$300 per person per year, making it cheaper than other HIV therapeutic medications and making it possible to use it in developing countries as well.

WO 02/072081

It is evident from the above results and discussion that the subject invention provides for a number of advantages in the delivery of DTH inducing agents. The subject topical preparations are efficient and effective delivery vehicles for administration of a DTH inducing agent to a subject, and need only be applied for a short period of time in order to provide the agent administration. Furthermore, the subject topical patch preparations are 25°C storage stable. The subject preparations represent a low cost way of treating many disease conditions, including AIDS. As such, the subject invention represents a significant contribution to the art.

10

All publications and patents cited in this specification are herein incorporated by reference as if each individual publication or patent were specifically and individually indicated to be incorporated by reference. The citation of any publication is for its disclosure prior to the filing date and should not be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention.

15

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it is readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

20

WHAT IS CLAIMED IS:

1. A topical patch preparation of a delayed-type hypersensitivity inducer, said
5 preparation comprising:
an adhesive gel composition comprising a delayed-type hypersensitivity inducer; and
a support.
2. The topical patch preparation according to Claim 1, wherein said delayed-type
10 hypersensitivity inducer is 1-Chloro-2,4-Dinitrobenzene (DNCB).
3. The topical patch preparation according to Claim 2, wherein said DNCB is present in
said adhesive gel composition in an amount ranging from about 0.01 to 10.0 % (w/w).
- 15 4. The topical patch preparation of Claim 1, wherein said adhesive gel composition
comprises:
a water-soluble polymer gel;
water; and
a water retaining agent.
- 20 5. The topical patch preparation according to Claim 4, wherein said water is present in
an amount ranging from about 10 to 80 % (w/w).
6. The topical patch preparation according to Claim 1, wherein said adhesive gel
25 composition has a pH ranging from about 4.0 to 7.0.
7. The topical patch preparation according to Claim 1, wherein said adhesive gel
composition further comprises an organic solvent.
- 30 8. The topical patch preparation according to Claim 7, wherein said organic solvent is
selected from the group consisting of n-methyl-2-pyrrolidone, polyethylene glycol and
crotamiton and combinations thereof.

WO 02/072081

9. A topical patch preparation comprising:

(a) an adhesive gel composition having a pH ranging from about 4.0 to 7.0 and comprising:

- (i) DNCB in an amount ranging from about 0.01 to 10.0 % (w/w);
- (ii) a water-soluble polymer gel;
- (iii) water in an amount ranging from about 10 to 80 % (w/w); and
- (iv) a water retaining agent; and

(b) a support.

10. The topical patch preparation according to Claim 9, wherein said DNCB is present in an amount ranging from about 0.1 to 5.0 % (w/w).

11. The topical patch preparation according to Claim 10, wherein said DNCB is present in an amount ranging from about 0.2 to 3.0% (w/w).

12. The topical patch preparation according to Claim 9, wherein said water is present in an amount ranging from about 20 to 70% (w/w).

13. The topical patch preparation according to Claim 12, wherein said water is present in an amount ranging from about 30 to 60 % (w/w).

14. The topical patch preparation according to Claim 9, wherein said pH ranges from about 4.0 to 6.0.

15. The topical patch preparation according to Claim 14, wherein said adhesive gel composition further comprises an organic solvent.

16. The topical patch preparation according to Claim 15, wherein said organic solvent is selected from the group consisting of n-methyl-2-pyrrolidone, polyethylene glycol, and crotamiton and combinations thereof.

17. A topical patch preparation comprising:

- (a) an adhesive gel composition having a pH ranging from about 4.0 to 6.0 and comprising:
- (i) DNCB in an amount ranging from about 0.2 to 3.0 % (w/w);
 - (ii) a water-soluble polymer gel;
 - 5 (iii) water in an amount ranging from about 30 to 60 % (w/w);
 - (iv) a water retaining agent; and
 - (v) an organic cosolvent selected from the group consisting of n-methyl-2-pyrrolidone, polyethylene glycol and crotamiton and combinations thereof;
- 10 (b) a support.

18. A method of delivering a delayed-type hypersensitivity inducer to a subject, said method comprising:

- (a) applying a topical patch preparation comprising:
- 15 (i) an adhesive gel composition comprising said delayed-type hypersensitivity inducer; and
 - (b) a support;
- to a skin surface of said subject; and
- (b) maintaining said topical patch preparation on said skin surface for a period of
- 20 time sufficient for said delayed-type hypersensitivity inducer to be delivered to said subject.

19. The method according to Claim 18, wherein said delayed-type hypersensitivity inducer is DNCB.

25 20. The method according to Claim 19, wherein said DNCB is present in said adhesive gel composition in an amount ranging from about 0.01 to 10.0 % (w/w).

21. The method according to Claim 18, wherein said adhesive gel composition comprises:
- 30 a water-soluble polymer gel;
 - water; and
 - a water retaining agent.

22. The method according to Claim 21, wherein said adhesive gel composition further comprises an organic solvent.

23. The method according to Claim 22, wherein said organic solvent is selected from the group consisting of n-methyl-2-pyrrolidone, polyethylene glycol and crotamiton and combinations thereof.

24. The method according to Claim 18, wherein said method is a method of treating an immunocompromising disease.

25. A method of treating a host suffering from an immunocompromising disease, said method comprising:

(a) applying a topical patch preparation comprising:

(i) an adhesive gel composition comprising an effective amount of a delayed-type hypersensitivity inducer; and

(b) a support;

to a skin surface of said subject; and

(b) maintaining said topical patch preparation on said skin surface for a period of time sufficient for said effective amount of delayed-type hypersensitivity inducer to be delivered to said subject.

26. The method according to Claim 25, wherein said delayed-type hypersensitivity inducer is DNCB.

27. The method according to Claim 26, wherein said DNCB is present in said adhesive gel composition in an amount ranging from about 0.01 to 10.0 % (w/w).

28. The method according to Claim 25, wherein said adhesive gel composition comprises:

a water-soluble polymer gel;

water; and

a water retaining agent.

29. The method according to Claim 28, wherein said adhesive gel composition further comprises an organic solvent.

30. The method according to Claim 29, wherein said organic solvent is selected from the group consisting of n-methyl-2-pyrrolidone, polyethylene glycol and crotonamiton and combinations thereof.

31. The method according to Claim 25, wherein said immunocompromising disease is an HIV infection.

32. A method of treating a host suffering from an HIV infection, said method comprising:

(a) applying a topical patch preparation comprising:

(i) an adhesive gel composition comprising an effective amount of DNCB; and

(b) a support;
to a skin surface of said subject; and

(b) maintaining said topical patch preparation on said skin surface .

33. The method according to Claim 32, wherein said DNCB is present in said adhesive gel composition in an amount ranging from about 0.01 to 10.0 % (w/w).

34. The method according to Claim 32, wherein said adhesive gel composition comprises:

a water-soluble polymer gel;
water; and
a water retaining agent.

35. The method according to Claim 34, wherein said adhesive gel composition further comprises an organic solvent.

36. The method according to Claim 35, wherein said organic solvent is selected from the group consisting of n-methyl-2-pyrrolidone, polyethylene glycol and crotonamiton and combinations thereof.

5 37. A kit for use in transdermal delivery of a delayed-type hypersensitivity inducer to a subject in need thereof, said kit comprising:

(a) a topical patch preparation comprising:

(i) an adhesive gel composition comprising an effective amount of a delayed-type hypersensitivity inducer; and

10 (ii) a support; and

(b) instructions for using said preparation.

38. The kit according to Claim 37, wherein said kit comprises a plurality of said topical patch preparations.

15

39. The kit according to Claim 38, wherein said plurality of topical patch preparations are present in separate containers.

40. The kit according to Claim 39, wherein said separate containers are sealed pouches.

20

FIGURE 1

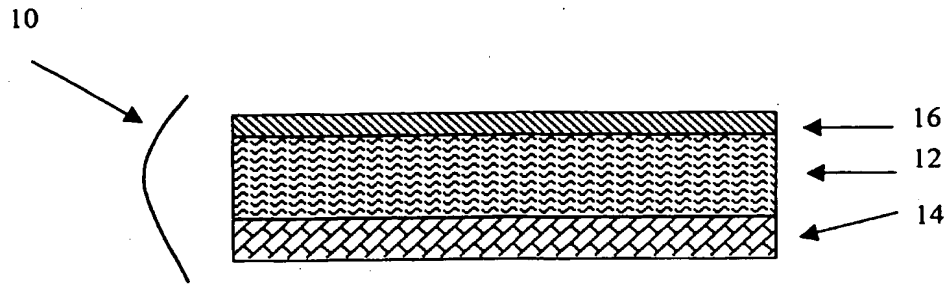


FIGURE 2

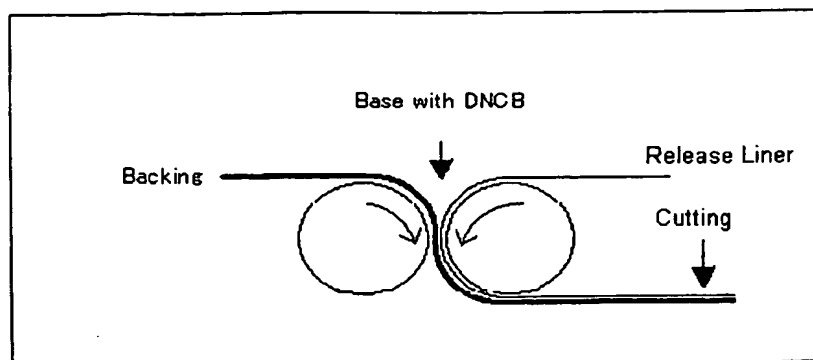
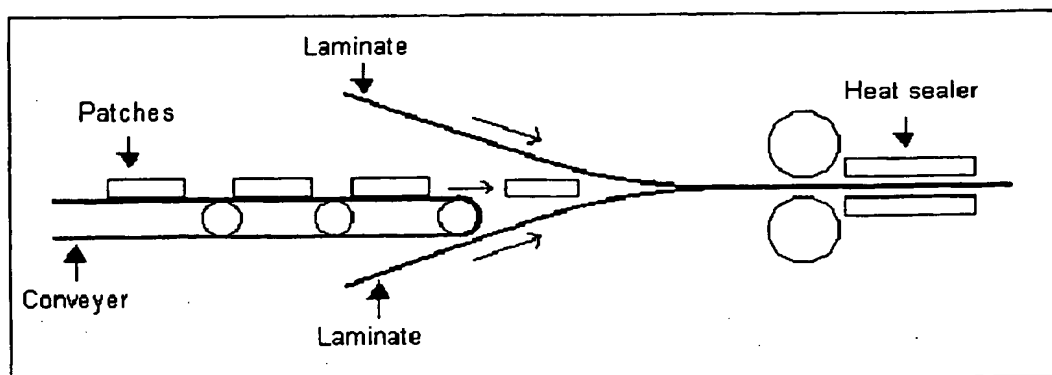


FIGURE 3



INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/05641

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/04 A61K9/70 A61P31/18 A61P37/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, CHEM ABS Data, PASCAL, EMBASE, SCISEARCH, LIFESCIENCES

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US 5 846 559 A (HOPP ROBERT B) 8 December 1998 (1998-12-08) * see in particular column 2, line 59 - column 3, line 14; column 3, lines 27-29; column 3, line 63 - column 4, line 19; column 5, line 57 - column 6, line 42; claims 1, 3, 5, 6-10 *	1-25, 37-40 26-36
X Y	US 4 214 592 A (JACQUET PIERRE ET AL) 29 July 1980 (1980-07-29) * see in particular column 4, lines 10-35; column 4, line 61 - column 5, line 45; column 7, lines 4-8; claims 1 and 7 *	1-23, 37-40 24-36

-/--

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

S document member of the same patent family

Date of the actual completion of the international search

30 July 2002

Date of mailing of the international search report

27/08/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Rodriguez-Palmero, M

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 02/05641

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 129 647 A (KLEIN EDMUND) 12 December 1978 (1978-12-12)	1-23, 37-40
Y	* see in particular column 2, lines 50-59; column 3, lines 8-15; column 6, line 66 - column 7, line 3; column 7, lines 21-24, 51-57 and 62-66; column 8, lines 14-19; column 9, lines 23-31 *	24-36
Y	----- ORACION RENATO ET AL: "DNCB treatment of HIV-infected patients leads to beneficial immunologic outcomes, reduced viral load, and improved measures of quality-of-life." JOURNAL OF INVESTIGATIVE DERMATOLOGY, vol. 110, no. 4, April 1998 (1998-04), page 476 XP001095435 Annual Meeting of the International Investigative Dermatology; Cologne, Germany; May 7-10, 1998 ISSN: 0022-202X * abstract *	1-40
Y	----- STRICKER R B ET AL: "Decrease in viral load associated with topical dinitrochlorobenzene therapy in HIV disease." RESEARCH IN VIROLOGY, vol. 148, no. 5, 1997, pages 343-348, XP002208068 ISSN: 0923-2516 * see in particular the abstract; page 345, table I; page 346, table II *	1-40
P,Y	----- EP 1 170 020 A (TEIKOKU SEIYAKU KK) 9 January 2002 (2002-01-09) * see in particular page 2, paragraph 9; page 3, paragraph 19 - page 4, paragraph 27; page 4, paragraph 32 *	1-40
A	----- EP 0 782 861 A (HISAMITSU PHARMACEUTICAL CO) 9 July 1997 (1997-07-09) * see in particular page 2, lines 26-41; page 4, lines 25-52; page 8, lines 18-27 *	1-40
A	----- EP 1 029 542 A (TAISHO PHARMA CO LTD) 23 August 2000 (2000-08-23) * see in particular page 3, paragraph 20; page 4, example 1 *	1-40

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

Continuation of Box I.1

Although claims 18-36 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/05641

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 02/05641

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5846559	A	08-12-1998	US 2001051182 A1 AU 5543196 A WO 9632142 A1	13-12-2001 30-10-1996 17-10-1996
US 4214592	A	29-07-1980	FR 2375861 A1 AT 359208 B AT 942677 A BE 862515 A1 CA 1100870 A1 CH 627646 A5 DE 2755838 A1 DK 587177 A ,B, ES 238689 Y ES 465611 A1 GB 1570550 A IT 1089296 B JP 1366298 C JP 53085983 A JP 61029933 B LU 78803 A1 NL 7714612 A ,B, NO 774527 A ,B, SE 421377 B SE 7714962 A	28-07-1978 27-10-1980 15-03-1980 30-06-1978 12-05-1981 29-01-1982 06-07-1978 01-07-1978 16-05-1979 01-01-1979 02-07-1980 18-06-1985 26-02-1987 28-07-1978 10-07-1986 20-07-1979 04-07-1978 03-07-1978 21-12-1981 02-07-1978
US 4129647	A	12-12-1978	US 4211767 A	08-07-1980
EP 1170020	A	09-01-2002	EP 1170020 A1 WO 0147559 A1	09-01-2002 05-07-2001
EP 0782861	A	09-07-1997	AU 3618795 A DE 69524614 D1 EP 0782861 A1 JP 3184534 B2 KR 209469 B1 US 5891920 A ES 2167463 T3 WO 9611022 A1	02-05-1996 24-01-2002 09-07-1997 09-07-2001 15-07-1999 06-04-1999 16-05-2002 18-04-1996
EP 1029542	A	23-08-2000	JP 11171768 A AU 738789 B2 AU 9559798 A CA 2306479 A1 EP 1029542 A1 US 6355266 B1 CN 1278723 T WO 9918955 A1	29-06-1999 27-09-2001 03-05-1999 22-04-1999 23-08-2000 12-03-2002 03-01-2001 22-04-1999

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☒ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.